UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,529	09/09/2003	Ronald J. Graham	375461-007US	4786

37509 7590 10/16/2007

DECHERT LLP
P.O. BOX 390460
MOUNTAIN VIEW, CA 94039-0460

EXAMINER	
LEE, JAE W	
ART UNIT	**PAPER NUMBER**
1656	
MAIL DATE	**DELIVERY MODE**
10/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,529	GRAHAM ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/30/2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *28,29,31,32 and 35-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27, 30, 33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 01/29/2007), Applicants filed a response and amendment received on 07/30/2007. Said amendment amended Claim(s) 2, 4, 6-8, 14, 18, 22, 34, 39, 43, 44, 49, 53 and 54. Thus, Claim(s) 1-55 is/are at issue and present for examination.

Applicants' arguments filed on 07/30/2007, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

It is noted by the Examiner that Claim(s) 28, 29, 31, 32 and 35-55 is/are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention in the previous Office actions, a non-Final rejection (mailed on 01/29/2007).

Drawings

The previous objection to drawings for missing labels for Y-axis and X-axis in Fig. 7B is withdrawn by virtue of Applicants' amendment.

Claim Objections

The previous objection of Claim 4 for misspelling is withdrawn by virtue of Applicants' amendment.

Claims 5 and 6 are objected to because of the following informalities:

Claims 5 and 6 are objected to because the recitation of "TK", "AGC", "CAMK", "CMGC", "STE", "TKL", "CKI", "Src", "Lyn", "Fyn", "Akt", "MAP" and "MAPKAP2" should be in parenthesis and follow the phrase it abbreviates when used for the first time.

Applicants argue that these abbreviations are terms that are recognized in the art, therefore are well known and understood by the skilled artisan.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Above-mentioned recitations of abbreviations are required to be written out in full because, for instance, the term "TK" could stand for tyrosine kinase or thymidine kinase. The Examiner suggests Applicants improve the clarity of the claims by writing out what these abbreviations represent in full when used for the first time.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase, "enzyme recognition moiety," which is unclear. It is unclear with respect to what Applicants intend as being encompassed by the phrase.

Applicants point out that "support for "enzyme recognition moiety" is found through out the specification, for example at paragraphs 29-31.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the Examiner notes that in paragraph [0031] it is stated that:

> "In one embodiment, the enzyme recognition moiety comprises a polypeptide segment that contains a group that is chemically altered by the enzyme during the assay to cause an increased fluorescent signal. In some embodiments, the recognition moiety comprises at least 3, 4, 5, 6 or 7 amino acid residues."

However, such statements of what the phrase embody, do not clearly define what is included and what is excluded in the scope of said phrase. For instance, in some other embodiment, "the enzyme recognition moiety" could comprise phosphates or glycosylations and not contain any amino acid residue.

Claim 5 recites the phrase, "to the group "other"," which is unclear. It is unclear with respect to what Applicants mean by the phrase.

Applicants argue that the term "other" recited in Claim 5 is an art recognized term that refers to certain types of protein kinases. To support Applicant's position, enclosed herein as Exhibit A is an excerpt of a supplementary table by Manning et al., 2002, "The protein kinase complement of the human genome." Science 298(5600):1912-34, in which "Other" is identified as a specific group of protein kinases.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The group "other" according to the reference of Manning et al. is indicating that these genes are not yet classified, therefore the reference does not define a specific group called "other" that is made up of homologs or orthologs based on their structural and/or functional similarities. As such, the term "other" is still unclear and indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27, 30, 33 and 34 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-27, 30, 33 and 34. In response to this rejection, Applicants have amended claims 2, 4, 6-8, 14, 18, 22, 34, and traversed the rejection as it applies to the newly amended claims.

Applicants argue that written description for each of the elements of Claim 1 is found throughout the specification by pointing to supports in the specification: For example, support for a hydrophobic moiety capable of integrating the substrate compound into a micelle can be found at ¶¶ 21, 68-71 and 124, and examples of hydrophobic moieties can be found at ¶ 72 (C6-C26 n-alkyl chains); Scheme 1, ¶ 137 and Scheme 2, ¶ 143 (a C-16 fatty acid acyl group (palmitoyl)); Scheme 3, ¶ 151 and Table 2 (dodecanoyl, tetradecanoyl, nonanoyl groups); Scheme 4, ¶ 153 (a hydrophobic moiety substituted by at least one halogen atom, e.g., n-(1H, 1H, 2H, 2H perfluorodecyl-l-thiol-2-acetyl)); Scheme 5, ¶ 156 (N-perfluoro-octanoyl); Scheme 6, ¶ 159 (an octadecanoyl group); Table 3 provides additional examples of hydrophobic moieties (C13, C15 and C 17); and Scheme 7, ¶ 165 (a hexadecanoyl group). Further Applicants point to support for "fluorescent moiety," which can be found at: ¶¶ 11 and 73-90, and examples of fluorescent moieties can be found at ¶ 11 (sulfofluorescein and rhodamine); ¶¶ 75-80 (xanthine substituted ring); ¶¶ 81-82 (rhodamine-type substituted ring); ¶¶ 83-84 (substituted or unsubstituted fluorescein-type ring); ¶ 85 (orthocarboxyrhodamines); ¶ 86 (4,7-dichlororhodamines, rhodamine B, 5-carboxyrhodamine, rhodamine X (ROX), 4,7-dichlororhodamine X (dROX), rhodamine 6G (R6G), 4,7-dichlororhodamine 6G, rhodamine 110 (R110), 4,7-dichlororhodamine

110 (dR110), tetrarnethylrhodamine (TAMRA) and 4,7-dichlorotetramethylrhodamine (dTAMRA) and 4,7-dichloro- orthocarboxyrhodamine); ¶¶ 85 (fluorescein-type ring in which C9 is substituted with an orthocarboxy phenyl substituent); ¶ 88 (4,7-dichlorofluoresceins, 5-carboxyfluoresceine (5-FAM), 6-carboxyfluorescein (6-FAM), and 4,7-dichloro-ortho-carboxyfluorescein); ¶ 89 (cyanine, phthalocyanine, squaraine and bodipy dye); ¶ 153 (5-carboxysulfofluorescein); ¶ 156 (5-carboxy-. 2',7'-dipyridyl-sulfofluorescein); and ¶ 163 (2',7'-dichloro-5-carboxy-4,7-dichlorofluorescein); in addition to other examples of fluorescent moieties are incorporated by reference at ¶¶ 88 and 91. Applicants further point to support for "an enzyme recognition moiety," which can be found at ¶¶ 29-31, 61-67, and 118-123, and examples of enzyme recognition moieties can be found at ¶¶ 67 and 123, Schemes 1-7 and Tables 1 and 3. Also, Applicants point out working examples showing the actual reduction to practice of various embodiments of the claimed substrate compounds can be found in Examples 1-11. Therefore, Applicants allege, in view of the disclosure cited above, Applicant has described the claimed invention using words, structures, figures, diagrams, and formulas that fully set forth the claimed invention, and also has provided several actual reductions to practice.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The reason is that the claimed genera of substrate compounds encompass structures that are widely variant, and the disclosed species as mentioned above simply do not represent the claimed genera. For instance, Applicants fail to describe the genera of substrate compounds comprising any

hydrophobic moiety, any enzyme recognition moiety, and any fluorescent moiety, wherein said hydrophobic moiety is a hydrophobic amino acid methionine, said enzymatic recognition moiety is a threonine, and said fluorescent moiety is an amino acid residue capable of fluorescing such as tyrosine or phenylalanine. Taken together, the genera of substrate compounds comprising any hydrophobic moiety capable of integrating the compound into a micelle, any fluorescent moiety and any enzymatic moiety encompass widely variant species, having essentially any structure. Please refer to the M.P.E.P. section 2163 [R-5] under II, A, 3, (a), (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus. For the reasons described herein and in the previous office action, the rejection under this statute is maintained.

Claims 1-27, 30, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for substrate compounds having different length alkylacyl groups prepared in both phosphorylated and unphosphorylated form, represented by the following formula: X-Y(Dye)LRRASLG-NH_2, wherein X is a fatty acid acyl group of the form $CH_3(CH_2)_xC(=O)$-, x is 0, 7, 10, or 14, Y is alpha-aminomethyl glycine, Dye is a 4,7-dichlorofluorescein dye attached to the 2-amine nitrogen atom of Y by a 5- carbonyl linkage to the pendant phenyl ring of the dye, wherein the enzyme recognition moiety consisting of amino acid sequence RRASL capable of being phosphorylated by Protein Kinase A, does not reasonably provide enablement for any substrate compound

comprising any hydrophobic moiety capable of integrating the compound into a micelle, any fluorescent moiety, and any enzyme recognition moiety. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-27, 30, 33 and 34. In response to this rejection, Applicants have amended claims 2, 4, 6-8, 14, 18, 22, 34, and traversed the rejection as it applies to the newly amended claims.

Applicants argue that multiple, enabled uses of the claimed compounds are provided throughout the specification by pointing to Examples 1-11, which provide a plurality of reductions to practice within the scope of Claim 1. Applicants further point out that the Patent Office has acknowledged the enablement of a compound in phosphorylated and unphosphorylated form within the scope of the claimed invention. Thus, Applicants allege, in view of the above standard, that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention."

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. It is noted by the Examiner that the previous office action states, in order to comply with the rejection under this statute, the scope of the claims must be commensurate with the disclosure of the instant application, so that one of skill in the art can make and use the claimed invention. In the instant case, the disclosure of substrate compounds having different length alkylacyl groups prepared in

both phosphorylated and unphosphorylated form, represented by the following formula: X-Y(Dye)LRRASLG-NH_2, wherein X is a fatty acid acyl group of the form $CH_3(CH_2)_xC(=O)$-, x is 0, 7, 10, or 14, Y is alpha-aminomethyl glycine, Dye is a 4,7-dichlorofluorescein dye attached to the 2-amine nitrogen atom of Y by a 5- carbonyl linkage to the pendant phenyl ring of the dye, wherein the enzyme recognition moiety consisting of amino acid sequence RRASL capable of being phosphorylated by Protein Kinase A in the specification is not commensurate with the scope of the claims, which encompasses any substrate compound comprising any hydrophobic moiety capable of integrating the compound into a micelle, any fluorescent moiety, and any enzyme recognition moiety. Furthermore, the Examiner notes that the claimed invention is drawn to a product, and not to the "use." Thus, the statement, "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention," is irrelevant. For the reasons described herein and in the previous office action, the rejection under this statute is maintained.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the

> applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 8, 20, 21, 23, 27, 33 and 34 are rejected under 35 U.S.C. § 102(a) and 102(e) as being anticipated by Kramer et al. (USPN 7,049,080) because the reference of Kramer et al. has the publication date of 07/04/2002 and the filing date of 08/07/2001 respectively.

The rejection was stated in the previous office action as it applied to previous claims 1-27, 30, 33 and 34. In response to this rejection, Applicants have amended claims 2, 4, 6-8, 14, 18, 22, 34, and traversed the rejection as it applies to the newly amended claims.

Applicants argue that the claimed invention is drawn to three types of distinct moieties, and that Kramer et al. does not disclose the claimed hydrophobic moiety. Applicants allege that the mere statement that 6-TAMRA is "soluble" in DMSO and methanol without more is insufficient to support the rejection under 35 U.S.C. § 102. Applicants further allege that the Patent Office's position that TAMRA is "soluble" in DMSO and methanol and therefore inherently functions as the claimed hydrophobic moiety is unsubstantiated and the rejection should be withdrawn.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. It is noted by the Examiner that in paragraph [0069] on pg. 17-18, it is stated that the hydrophobic moiety's

"exact length, size and/or composition of the hydrophobic moiety can be varied to obtain the desired results. In one embodiment, the hydrophobic moiety comprises a hydrocarbon (consisting of carbon and hydrogen atoms) comprising from 6 to 30 carbon atoms, or from 6 to 25 carbon atoms, or from 6 to 20 carbon atoms, or from 6 to 15 carbon atoms, or from 8 to 30 carbon atoms, or from 8 to 25 carbon atoms, or from 8 to 20 carbon atoms, or from 8 to 15 carbon atoms, or from 12 to 30 carbon atoms, or from 12 to 25 carbon atoms, or from 12 to 20 carbon atoms. The hydrocarbon maybe linear, branched, cyclic, or any combination thereof."

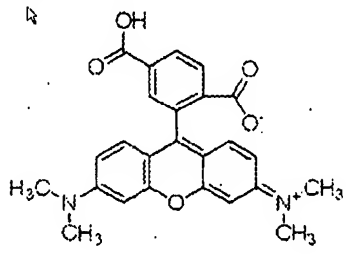
Therefore, in view of the above, and the fact that 6-TAMRA consists of $C_{25}H_{22}N_2O_5$ (see previously cited reference, showing it's molecular structure), 6-TAMRA is in the scope of the claimed "hydrophobic moiety."

Further, it is noted by the Examiner that the molecular structure of 6-TAMRA comprises multiple fused-heterocyclic ring structures, which are known in the art to be

www.sigma-aldrich.com

55222 6-Carboxytetramethylrhodamine

Fluka BioChemika, for fluorescence, >90% (HPLC)



hydrophobic. Therefore, the 6-TAMRA has a hydrophobic moiety regardless of its solubility in DMSO or methanol.

Furthermore, as shown in the evidentiary reference of Ouchi et al. (Design of attachment type of drug delivery system by complex formation of avidin with biotinyl drug model and biotiyl saccharide, Journal of Controlled Release, 2004, Vol. 94, pg. 281-291), 6-TAMRA is "capable of integrating the compound into a micelle" because it is shown that 6-TAMRA conjugate is capable of diffusing into HepG2 cells, which are micelles with phospholipid bilayer membranes (see Figure 7 on pg. 289, and pg. 288, right column, lines 6-18). Taken together 6-TAMRA is "a hydrophobic moiety capable of integrating the compound into a micelle." For the reasons described herein and in the previous office action, the rejection under this statute is maintained.

Double Patenting

The Applicants' statement, requesting "this rejection be held in abeyance until there is an indication of otherwise patentable subject matter" because "[o]nly at that time, will Applicant be able to assess the propriety of the rejection, is acknowledged.

Conclusion

Claims 1-27, 30, 33 and 34 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL.

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner: Jae W. Lee, Ph.D.

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER